

Cervical cerclage for preventing spontaneous preterm birth in twin pregnancies with transvaginal ultrasound cervical length \leq 15mm: a study protocol for a randomized clinical trial

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List of Abbreviations

AE: Adverse Event

CI: Confidence Interval

CL: Cervical Length

HIPAA: Health Insurance Privacy and Portability Act of 1996

IRB Institutional Review Board

PTB: Preterm Birth

RCT: Randomized Controlled Trial

SAE: Serious Adverse Event

TVU CL: Transvaginal ultrasound cervical length

UIC: Ultrasound indicated cerclage

Study Summary

Title	Cervical cerclage for preventing spontaneous preterm birth in twin pregnancies with transvaginal ultrasound cervical length \leq 15mm: a study protocol for a randomized clinical trial
Short Title	Cerclage for Twins with short cervix
Methodology	Multi-center, open label, randomized trial
Study Duration	3 years for subject enrollment, and an additional 6 months for analysis and manuscript preparation: 2017-2021
Study Center	Thomas Jefferson University
Objectives	The primary objective of this study is to determine if ultrasound indicated cerclage reduces the incidence of spontaneous preterm birth in asymptomatic women with twin gestations with transvaginal ultrasound cervical length \leq 15mm before 24 weeks of gestation.
Number of Subjects	200
Diagnosis and Main Inclusion Criteria	Women, age older than 18, with a twin gestation and transvaginal ultrasound cervical length \leq 15mm between 16 to 23 6/7 weeks gestation
Study Product and Planned Use	Cervical cerclage
Reference therapy	Standard obstetrical care include daily vaginal progesterone 400mg from diagnosis of cervical length \leq 25mm (usually 20 weeks) to 36 weeks
Statistical Methodology	Statistical analysis will be based on the intention-to-treat principle. The risk of spontaneous preterm birth before 34 weeks will be quantified by use of the odds ratio and 95% CI. Multivariate analysis will be performed using logistic regression.

1 Introduction

This document is a protocol for a human research study.

1.1 Background

The incidence of preterm birth (PTB) in the United States is 9.63% with 390,000 deliveries occurring at less than 37 weeks gestation annually, however the incidence of early preterm (less than 34 weeks) have remained steady at 2.76%, with this being the most vulnerable neonatal group.¹ Risk factors for spontaneous preterm births include a previous preterm birth, multiple pregnancies, black race, smoking, periodontal disease, low maternal body-mass index and short cervical length.^{1,2}

In 2015, the twin birth rate was 33.5 twins per 1000 total births. The twin birth rate increased steadily by 76% overall from 1980 to 2009. The number of twin births has risen substantially due to the increased use of assisted reproductive technology. Twin pregnancies have 59% incidence of PTB before 37 weeks and 10.7% incidence of PTB < 32 week, 10 times more at risk of low birth-weight infants (LBW) and had 5 times more risk of early neonatal death.^{1,3} The increased rate of preterm birth in twins is associated with increased neonatal morbidity and mortality rates. Disorders related to short gestation and LBW (low birth weight) is the second cause of infant death (17.2%).^{1,4}

In singleton pregnancies with risk factors for PTB, effective medical interventions have been identified to reduce the risk of recurrent PTB. In women with singleton pregnancy and history of PTB, weekly treatment with intramuscular 17-alpha hydroxyprogesterone caproate beginning at 16-20 weeks gestation until 36 weeks⁵ and ultrasound indicated cervical cerclage for women with transvaginal ultrasound cervical length (TVU CL) \leq 25mm identified before 24 weeks of gestation have shown effective to decrease PTB by 44% and 30% respectively.⁶ Women with singleton pregnancy with no history of PTB and incidental finding of cervical length \leq 25mm before 24 weeks of gestation will benefit from vaginal progesterone.⁷

Similar to singleton pregnancy, in twin pregnancy TVU CL \leq 25mm before 24 weeks of gestation identify women at risk of preterm birth.^{8,9} For example the calculated risk of PTB <36 week for a twin pregnancy with TVU CL \leq 25mm at 20 weeks is 83% while TVU CL \leq 15mm at the same gestational age is 94%, and the calculated risk of PTB < 32 weeks is 69% and 78% respectively. Several randomized clinical trials have evaluated the effectiveness of 17-alpha hydroxyprogesterone caproate,^{10 11, 12} vaginal progesterone, pessary or ultrasound indicated cervical cerclage¹³⁻¹⁵ in women with twin pregnancy TVU CL less than 25mm before 24 weeks with no significant difference between study vs control group. However, to date, no trial has evaluated the potential benefit of a cerclage in twins, specifically for women with a TVU CL \leq 15mm

1.2 Clinical Data to Date

Pessary:

A recent pessary trial conducted on women with twin pregnancy and TVU CL < 30mm at three institutions (TJUH, University of Pennsylvania and Naples, Italy) showed no significant decrease in the incidence of preterm birth <34 weeks or improvement in the perinatal outcome.¹⁶ Other similar trials in USA and Europe have shown conflicting results. A meta-analysis evaluating all available studies concluded that the use of the pessary in twin pregnancies with short TVU CL at 16-24 weeks does not prevent SPTB or improve perinatal outcome.¹⁷

Vaginal progesterone:

An Egyptian randomized clinical trial of twin gestation with TVU CL 20-25 mm between 20 to 24 weeks of gestation using daily 400mg vaginal progesterone versus no progesterone showed a significant 33% and 60% decrease in preterm labor <34 week: 41/116 (35.3 %) vs 57/108 (52.8 %) RR: 0.67 (0.49–0.90) and preterm labor <32 week: 14/116 (12.1 %) vs 32/108 (29.6 %) RR: 0.40 (0.23–0.72) respectively and 33% decreased in neonatal respiratory distress: 82/229 (35.8 %) vs 111/210 (52.9 %) RR: 0.67 (0.54–0.84).¹⁸

A recently published meta-analysis and individual patient database including 303 women (159 assigned to vaginal progesterone, 144 assigned to placebo/no treatment) and their 606 infants from six randomized controlled trials) concluded that the use of daily 400mg of vaginal progesterone in women with twin pregnancy and TVU CL ≤ 25 mm decreased the risk of preterm birth <34 week and <32 weeks by 29% and 49% respectively and decreased on composite neonatal morbidity and mortality by 47%: 23/84 (27.3%) vs 28/70 (40%) RR: 0.57 (0.36-0.93).¹⁹ This therapy seems to be more effective in twins with TVU CL 20 to 25mm (n=207) and maybe useful between 10-19mm (n=84), but a significant decrease in preterm birth was not seen when TVU CL is <10 mm (n=14), however the sample size in these last two subgroups were too small to conclude.

Based on this new information, we at the Maternal Fetal Medicine Division at TJUH considered that there is enough evidence to initiate routine screening for preterm birth with TVU CL in women with twin pregnancies from 18 to 24 weeks and to offer daily 400mg of vaginal progesterone to those women with TVU CL ≤ 25mm as a standard practice since February 2017.

Cervical cerclage:

Three randomized clinical trials with 49 twin gestations with a TVU CL ≤ 25 mm were included in an individual patient data meta-analysis (only 7 women had TVU CL ≤ 15 mm). Adjusting for previous preterm birth and gestational age at randomization, there were no statistically significant differences preterm birth <34 weeks (aOR 1.17, 95% CI 0.23-3.79) and neonatal outcomes. They conclude that cerclage cannot currently be recommended for clinical use in twin pregnancies with a maternal short cervical length in the second trimester and larger trials are still necessary.²⁰

A retrospective cohort of 140 women twin pregnancy with TVU CL ≤ 25mm before 24 weeks showed that cervical cerclage did not decrease the incidence of PTB < 34 weeks, however the subgroup of women twin pregnancy with very short TVU CL ≤ 15mm before 24 weeks (n=71) showed that cervical

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cerclage significantly decreased the PTB < 34 weeks by 49% from 30/39 (76.9%) to 15/32 (46%) aOR: 0.51 (0.31–0.83), with significant prolongation of pregnancy by almost 4 weeks and decreased admission to NICU by 59% from 63/75 neonates (84%) to 38/58 (65.5%) aOR: 0.41 (0.24–0.81).²¹

A second retrospective cohort study including 80 women with twin pregnancy and TVU CL \leq 25mm before 24 weeks showed that cervical cerclage decreased the PTB < 32 weeks by 60% from 20/60 (76.9%) to 15/32 (46%) (RR, 0.40 (95% CI, 0.20–0.80)).²²

These two studies were limited by the retrospective nature of the cohort, were originated from different institutions during several years of collection, and the overall management of the cases were different, therefore final recommendation cannot be made and a prospective randomized trial will be needed to corroborate these findings.

We hypothesized that women with twin pregnancy and asymptomatic TVU CL \leq 15mm identified before 23 6/7 weeks receiving a combination of daily vaginal progesterone and cervical cerclage will have significantly decreased preterm birth < 34 weeks, and will improved perinatal morbidity and mortality when compared with daily vaginal progesterone alone.

1.3 Risk/Benefits

The major risks of ultrasound indicated cerclage that have been reported in previous studies involving singleton pregnancies include intraoperative rupture of membranes (less than 1%), cervical laceration, cervical bleeding, chorioamnionitis (undiagnosed at the time of cerclage or acquired post cerclage placement), failure to place the cerclage and failure of the cerclage on prolonging pregnancy with possible pregnancy loss or delivery at a perivable gestational age around 23-25 weeks of gestation.²³ Other risks are those associated with anesthesia during the surgical procedure: hypotension, allergy to medications, headache. To limit these risks, the anesthetic route is typically regional anesthesia. Later on during the course of pregnancy, other risks maybe present as preterm contractions with the cerclage in place may cause laceration of the cervix and bleeding in which case the cerclage needs to be removed.

Minor side effects include increased vaginal discharge, there is a theoretical disruption the vaginal flora associated with foreign object, and minimal discomfort at the time of cerclage removal.

The potential benefits include prolongation of pregnancy, decreased very preterm delivery (< 28 weeks), very low birth weight (<1500 grams) and decreased in composite morbidity for the newborn (respiratory distress syndrome, need of intubation and mechanical ventilation, intraventricular hemorrhage, necrotizing enterocolitis, sepsis and retinopathy of the preterm newborn) and length of admission in the neonatal intensive care unit. Decreased perinatal mortality. These potential benefits are based on results of previous retrospective cohorts available in twin pregnancies.

All of the investigators have received formal training on ultrasound indicated cerclage placement. The training and experience of the investigators will minimize the risks associated with cerclage placement.

Our protocol specifically states that the cervical cerclage will be removed if the patient goes into labor, has preterm premature rupture of membranes (PPROM), presents with active cervical bleeding, or if she remains asymptomatic and reaches 36 weeks of gestation.

2 Study Objectives

The overall objective of this study is to assess the efficacy of the use of ultrasound indicated cerclage for prevention of preterm birth in a population of women with twin gestations and TVU CL \leq 15 mm prior to 23 6/7 weeks.

2.1 Primary Objective

The primary objective of this study is to determine if ultrasound indicated cerclage reduces the incidence of spontaneous PTB before 34 weeks in asymptomatic women with twin gestations and TVU CL \leq 15 mm between 16 0/7 to 23 6/7 weeks of gestation.

2.2 Secondary Objective

To determine if ultrasound indicated cerclage reduces the incidence of spontaneous PTB before 24, 28 and 32 weeks in asymptomatic women with twin gestations and TVU CL \leq 15 mm between 16 0/7 to 23 6/7 weeks of gestation.

To determine if ultrasound indicated cerclage reduces the neonatal mortality and morbidity in asymptomatic women with twin gestations and TVU CL \leq 15 mm between 16 0/7 to 23 6/7 weeks of gestation. Neonatal morbidity will include any of the following (composite neonatal outcome): respiratory distress syndrome (grade 3 or 4), need for intubation and mechanically assisted ventilation, intraventricular hemorrhage (grade 3 or 4), necrotizing enterocolitis (grade 3 or 4), proven sepsis diagnosed by culture, retinopathy of the preterm newborn requiring laser treatment (grade 3 or 4) and length of stay in the intensive care unit. Neonatal mortality will include any death before discharge from the hospital.

3 Study Design

3.1 General Design

This is a multi-center, open-label, randomized study. Women with twin gestations presenting for routine prenatal ultrasound between 16 to 23 6/7 weeks will be offered the option of having their cervical length measured as part of the standard of care for screening of preterm birth. Women with TVU CL \leq 25mm will be counseled about the risk of preterm birth and will be offered 400mg daily vaginal progesterone until 36 weeks of gestation. Those women with a cervix measuring \leq 15mm will be invited to participate in the trial. Eligible subjects can be enrolled between 16 0/7 to 23 6/7 weeks gestation; subjects randomized to the use of the ultrasound indicated cerclage will have the procedure scheduled in the operating room under anesthesia. Decision to perform amniocentesis prior to the cerclage to rule out subclinical chorioamnionitis, surgical technique and suture type will be at the discretion of the

surgeon. Once the ultrasound indicated cerclage is in place, subjects will continue with their usual scheduled clinical prenatal visits, and will participate in the study until delivery. Cerclage will be removed during the 36th week of pregnancy on those asymptomatic women or earlier if indicated (preterm labor, PPROM, vaginal bleeding). Newborns will participate in the study until discharge home from the hospital. Information about pregnancy and neonatal outcomes will be obtained from medical records.

3.2 Primary Study Endpoints

Spontaneous preterm delivery at less than 34 weeks gestation

3.3 Secondary Study Endpoints

Secondary effectiveness endpoints:

- Gestational age at delivery
- Interval between diagnosis and delivery
- Birth weight of each neonate
- Spontaneous preterm birth rates at less than 24, 28, 32 and 37 weeks gestation
- Spontaneous rupture of membranes before 34 weeks gestation

Secondary safety endpoints:

- Admission to the NICU and length of stay if admitted
- Neonatal death before discharge from hospital
- Composite adverse neonatal outcome (includes any of the following: necrotizing enterocolitis (grade 3 or 4), Intraventricular hemorrhage (grade 3 or 4), respiratory distress syndrome (grade 3 or 4), need for intubation and mechanically assisted ventilation, retinopathy of the newborn requiring laser treatment (grade 3 or 4), and proven sepsis with positive culture).
- Clinical Chorioamnionitis
- Histological chorioamnionitis (It is standard of care to send placenta to pathology for multiple gestations).
- Significant adverse maternal effects including intraoperative rupture of membranes, bleeding, and cervical laceration (tear).

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Pregnant women more than 18 years of age (limits the participants to female gender)
2. Diamniotic twin pregnancy
3. Asymptomatic
4. TVU CL \leq 15 mm between 16-23 6/7 weeks gestation

4.2 Exclusion Criteria

1. Singleton or higher order than twins multiple gestation
2. TVU CL >16mm
3. Cervical dilation with visible amniotic membranes
4. Amniotic membranes prolapsed into the vagina
5. Fetal reduction after 14 weeks from higher order
6. Monoamniotic twins
7. Twin-twin transfusion syndrome
8. Ruptured membranes
9. Major fetal structural anomaly
10. Fetal chromosomal abnormality
11. Cerclage already in place for other indication
12. Active vaginal bleeding
13. Clinical chorioamnionitis
14. Placenta previa
15. Painful regular uterine contractions
16. Labor

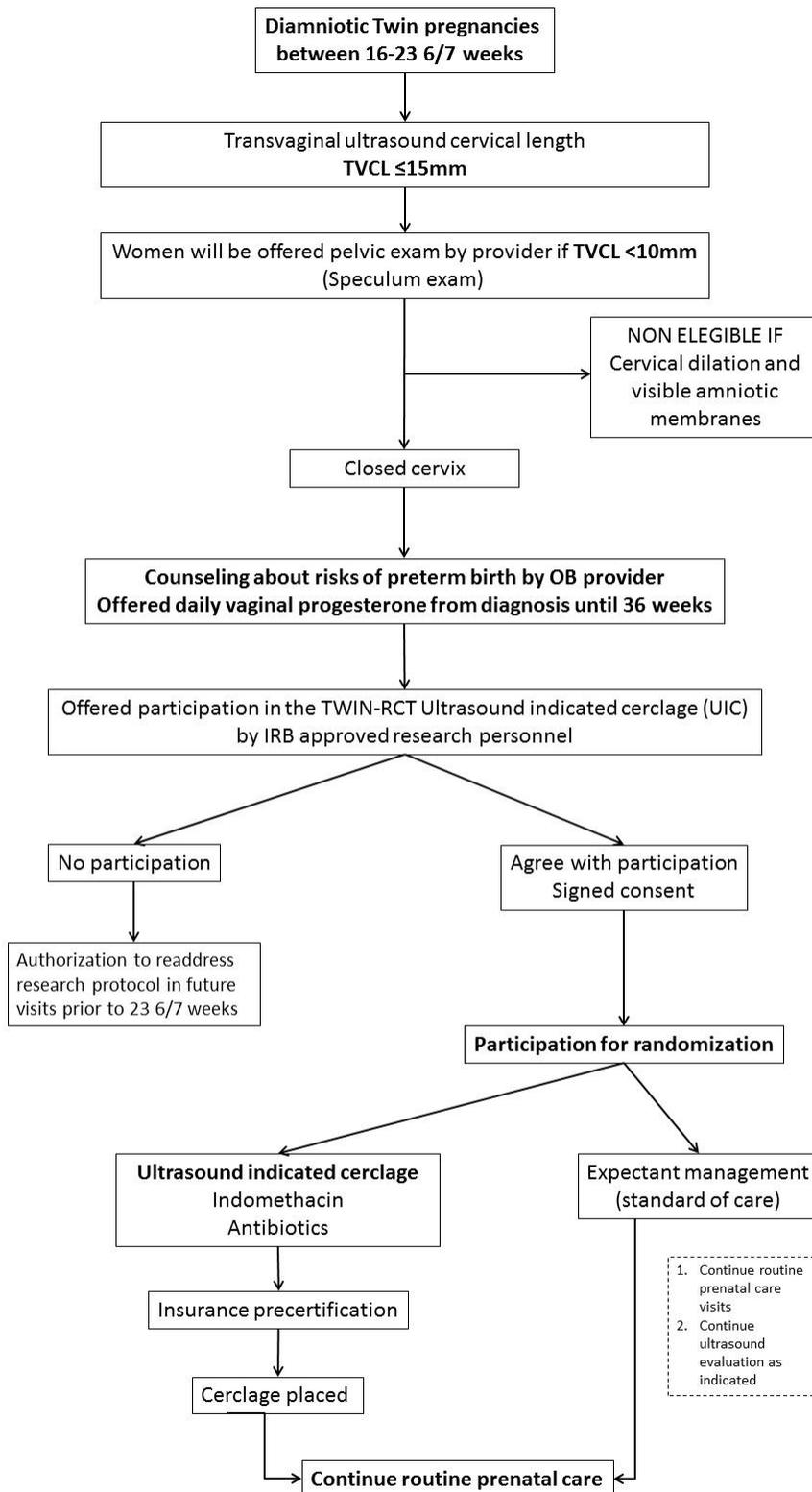
4.3 Subject Recruitment and Screening

1. Potential study subjects will be identified at the time of a routine second trimester fetal ultrasound exam between 18 to 23 6/7 weeks gestation. All clinical sites have designated prenatal ultrasound units. Patients at all sites diagnosed with twin gestation will be offered transvaginal ultrasound cervical length for the screening of preterm birth. The initial consent to have a transvaginal ultrasound assessment of the cervical length will be a verbal consent as part of standard of care.
2. Staff who will be performing screening TVU CL will be trained and certified through the Fetal Medicine Foundation <https://fetalmedicine.org/training-n-certification/certificates-of-competence/cervical-assessment-1> or CLEAR (<https://clear.perinatalquality.org/>).
3. TVU CL technique: Endocervical canal length will be measured as the distance between the internal and external os using a vaginal probe at 6-MHz probe placed in the anterior fornix of the vagina. Three anatomic landmarks will define the appropriate sagittal view: the internal os, the external os and the endocervical canal. The image will be enlarged while visualizing the three landmarks simultaneously. Gentle pressure will be exerted on the cervix by the transducer followed by minimal pressure to allow visualization of the three landmarks. This procedure will be repeated three times and the shortest measurement will be recorded.²⁴
4. Women with TVU CL \leq 25mm will be offered daily 400mg vaginal progesterone as standard of care based on recently published meta-analysis¹⁹ A repeat TVU CL will be offered a second time for those women with TVU CL 16 – 30 mm due to the concern for cervical length shortening over the next few weeks.

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5. Women with TVU CL ≤ 15 mm who will meet the inclusion criteria will be counselled by an obstetrician regarding the risk of SPTB as per standard of care. Only IRB approved research staff will approach eligible patients to assess interest in participating as well as to explain the trial. The patient will be given ample time to have all questions addressed and consider participation.
6. Women with a TVU CL < 10 mm will be offered a speculum exam (pelvic exam). If the cervix is dilated and amniotic membranes are visible, women would not be eligible for randomization in this clinical trial. A digital cervical exam will not be done routinely.
7. If the patient meets inclusion criteria and agrees to participate in the study, the informed consent form will be signed and a copy will be given to the patient.
8. Women who are eligible and consent to participate in the study will be randomly assigned to one of two groups: cervical cerclage (i.e. intervention group) or no cerclage (i.e. control group). A web-based system will be used to communicate the randomization assignments to the trial staff. Subjects will be randomized using blocks of randomly varying size (2, 4 and 6).
9. For those patients assigned to cerclage, an insurance precertification process will be requested. After insurance approves the procedure, the cerclage will be scheduled in the operating room and it will be placed by one of the Maternal Fetal Medicine specialist and fellow.
10. If patient declined participation and she is stable, she will continue outpatient bi-weekly or monthly prenatal care visits as per standard of care.
11. If patient elects to have expectant management without randomization, we will ask for her authorization to address the research protocol at a different opportunity during her prenatal visits until 23 6/7 weeks, after that gestational age she is no longer eligible for participation.

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5 Study

5.1 Description

Cervical cerclage is a suture/tape surgically placed around the cervix as close as possible to the high of the internal os. This suture is a non-absorbable sterile material

5.2 Treatment Regimens

Subjects will be randomized in a 1:1 fashion to either receive the ultrasound indicated cerclage, or expectant management. Women will still be able to withdrawal from the study after randomization if they feel that either expectant management or cerclage have an unacceptable risk of extreme premature delivery with increased risk of a severely handicap children.

5.2.1 Ultrasound indicated cerclage

For those randomized to ultrasound indicated cerclage placement, the surgical procedure will be scheduled in the main operating room under anesthesia.

5.2.2 Expectant management

For those randomized to expectant management, they will continue routine pregnancy care: daily vaginal progesterone and surveillance for signs of preterm labor.

5.3 Method for Assigning Subjects to Treatment Groups

A computer system will be used to communicate the randomization assignments to the trial staff. Subjects will be randomized centrally using blocks of randomly varying size (e.g, 2, 4 and 6).

5.4 Placement of Cerclage

Ultrasound indicated cerclage is placed by trained physician in the operating room under anesthesia (regional or general at the discretion of the anesthesiologist). Amniocentesis to evaluate for subclinical chorioamnionitis will be offered to every patient, declining amniocentesis doesn't exclude subjects from participation in this trial. Amnioreduction (removal of larger amount of amniotic fluid), surgical technique, election of sutures, and admission to the hospital for observation or recommended amount of maternal physical activity after randomization will be at the discretion of the attending physician performing the cerclage. Women randomized to the cerclage group will receive indomethacin 50mg orally before the cerclage and for three additional doses postoperatively every 8 hours (at 8h, 16h, and 24h after the cerclage). Women randomized to the cerclage group will also receive one dose of cefazolin 1g IV (or 2g if >80kg) before the cerclage.

6 Study Procedures

6.1 Transvaginal cervical length measurement

Potential study subjects will be identified in the ultrasound room. Transvaginal ultrasound cervical length will be offered at the time of a routine second trimester fetal anatomy ultrasound exam between 16-23 6/7 weeks gestation as part of standard of care practice for twin pregnancies, verbal consent will be requested prior to transvaginal ultrasound.

6.2 Randomization

Patients with TVU CL \leq 15mm who are eligible and consent to participate in the study will be randomly assigned to one of two groups: Ultrasound indicated cerclage or no cerclage (standard expectant obstetric management). Subjects will be randomized using random block sizes of 2, 4 or 6. Patients allocated to the ultrasound indicated cerclage group will have the cerclage surgically placed.

6.3 Interim Contacts

Patients in both groups will be contacted by the research assistants monthly either by phone or in person at the time of their prenatal visit. The research assistants will ask the patients if they have had any complications with their pregnancy including any evaluations and/or admissions for preterm labor, vaginal bleeding, leaking of amniotic fluid, vaginal discharge and/or discomfort of if they received medications like antenatal steroids for fetal lung maturity, tocolysis or magnesium sulfate infusion. Consents for release of medical information will be signed at the time of randomization to gather medical information pertinent to the study in case of admissions to other institutions.

Patients will be instructed to report any adverse symptoms including pain, vaginal bleeding, uterine contractions, decreased fetal movements and leakage of amniotic fluid immediately. They will be given a phone number to call if they have any questions or concerns about the study. A physician who is knowledgeable about the study will be available at all times. The study investigator will communicate with the patient's primary obstetrician; ultrasound indicated cerclage placement will be done by one of the study investigators, but removal at any time during pregnancy can be done by the primary obstetrician. The primary obstetrician will be responsible for all prenatal care and delivery.

6.4 Cerclage Removal

The cerclage will be removed by the primary obstetrician during the 36th week of gestation if asymptomatic. Removal of cerclage can be performed in the office or triage room; there is no need of anesthesia. Indications for cerclage removal before this time include: active vaginal bleeding, persistent uterine contractions despite tocolysis, ruptured of amniotic membranes, and prolapsed membranes through the cervix / suture.

6.5 Pregnancy Outcome

After subjects have delivered, information regarding outcome of the pregnancy and neonatal outcome until discharge home will be abstracted from the subjects' medical records. A release of medical records consent will be signed at the time of randomization, in case the patient delivers at an outside institution.

7 Statistical Plan

7.1 Sample Size Determination

Calculation of sample size was based on a reduction in the incidence of spontaneous delivery before 34 weeks from 70% in the expectant management group to 50% in the cerclage group, with a power of 80%. To detect this difference at a significance level of 5%, we will need to enroll a total of 186 subjects with 93 subjects in each arm, plus 10% for loss of follow up. Total 200 subjects with 100 subjects in each arm

7.2 Statistical Methods

The primary outcome is spontaneous preterm birth before 34 weeks of gestation. Secondary outcomes include gestational age at delivery, interval between diagnosis and delivery, birth weight, spontaneous preterm birth rates at less than 24, 28, 32 and 37 weeks gestation and spontaneous rupture of membranes at less than 34 weeks gestation. Secondary safety outcomes include admission to NICU, neonatal death, length of stay in the NICU until discharge home, composite adverse neonatal outcome that includes necrotizing enterocolitis (stage 3 or 4), intraventricular hemorrhage (grade 3 or 4), respiratory distress syndrome (grade 3 or 4), need of intubation and mechanical ventilation, retinopathy of prematurity requiring laser treatment (stage 3 or 4) and proven sepsis requiring treatment), and significant adverse maternal effects will include: intraoperative rupture of membranes, clinical or histological chorioamnionitis, postpartum hemorrhage, cervical tear and uterine rupture). Neonatal mortality prior to discharge home from the hospital.

Statistical analysis will be based on the intention-to-treat principle. Comparisons between the two groups will be made with the Mann-Whitney U test. Univariate comparisons of dichotomous data will be performed with Fishers exact test. The p values for all hypotheses will be two sided, and p values of less than 0.05 will be considered to be significant. The risk of spontaneous preterm birth before 34 weeks will be quantified by use of the relative ratio and 95% confidence interval. Multivariate analysis will be performed using logistic regression. The risk of spontaneous preterm birth from randomization until delivery will be assessed with Kaplan-Meier analysis, in which gestational age is the timescale, spontaneous delivery is the event, and elective deliveries are censored. SPSS software package (version 16.0) will be used for all statistical analyses.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)

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- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Unanticipated Adverse Surgical procedure Effect

An Unanticipated Surgical procedure Effect is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a surgical procedure, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a that relates to the rights, safety, or welfare of subjects.

Serious injury

Any injury or illness that is any one of the following:

- Life-threatening
- Results in permanent impairment of a body function or permanent damage to body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse effect related to the surgical procedure
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

What will be monitored:

Stopping rules: Any unanticipated effects and all adverse effects resulting in research subject death or injury will be reported to the PI immediately, no later than 10 days after the event and will include:

1. Maternal sepsis with admission to ICU attributable to the cerclage placement
2. Maternal death attributable to the cerclage placement
3. Maternal bleeding requiring blood transfusion attributable to cerclage placement

4. Fetal and/or neonatal death or injury attributable to the cerclage placement

Frequency of monitoring reports: after approximately 50% of the subjects have delivered

8.2 Recording of Adverse Effects

At each contact with the subject, the investigator must seek information on adverse effects by specific questioning and, as appropriate, by examination. Information on all adverse surgical procedure effects should be recorded immediately in the source document, and also in the appropriate adverse effect module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse effects occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse effects that occur after the study period should be recorded and reported promptly (see section 8.3 below).

The minimum initial information to be captured in the subject's source document concerning the adverse effect includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment
- Current status
- Whether study treatment was discontinued
- Whether the event is serious and reason for classification as serious

8.3 Reporting of Adverse Effects and Unanticipated Problems

8.3.1 Investigator reporting: Notifying the principal investigator

Principal investigator and DSM person contact information for reporting purposes
Report adverse effects by phone and facsimile to:

Amanda Roman-Camargo, MD
Email: amanda.roman@jefferson.edu

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Phone: 215-955-9200
Fax 215-955-5041

Stuart Weiner, MD
Email: Stuart.Weiner@jefferson.edu
Phone: 215-955-9200
Fax 215-955-5041

Adverse Effects

Any adverse effect that results in serious injury or death, and any type of unanticipated adverse effect, regardless of seriousness or severity, must be reported to the principal investigator by telephone within 24 hours of the event.

Within the following 48 hours, the principal investigator shall provide further information, as applicable, on the unanticipated adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the principal investigator.

Deviations from the study protocol

Deviations from the protocol must receive both principal investigator and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without principal investigator and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Principal investigator and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

Withdrawal of IRB approval

An investigator shall report to the principal investigator a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

8.3.2 Investigator reporting: Notifying the IRB

Adverse Effects

All unanticipated effects and all adverse effects resulting in research subject death or injury reported by the investigator to the study Principal investigator must also be reported to the investigator's local IRB in accordance with their reporting requirements, though no later than 10 working days.

Protocol Deviations

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Any protocol deviations initiated without principal investigator and/or the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Principal investigator and to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

Any adverse event that occurs any time during or after the research study, which in the opinion of the principal investigator is:

- Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document

AND

- Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator, the event was more likely than not to be caused by the research procedures.)

The above is required regardless of whether the event is serious or non-serious, on-site or off-site

Adverse Effects

All unanticipated effects and all adverse effects resulting in research subject death or injury must be reported to the investigator's local IRB in accordance with their reporting requirements, though no later than 10 working days.

Protocol Deviations

Any protocol deviations initiated without principal investigator and/or IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the investigator's IRB as soon as a possible, but no later than 5 working days of the protocol deviation.

Reporting Process

Report unanticipated problems as defined above to the IRB office as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:

For clinical trials, the following events are also reportable to the IRB:

- Any adverse event that would cause the principal investigator to modify the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
 - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
 - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
 - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

Unanticipated Adverse Effects

Evaluation

The principal investigator shall immediately evaluate each Unanticipated Adverse Effect. Such evaluations shall be reported to the IRB office, and participating investigators, within 10 working days after the principal investigator first receives notice of the effect.

Unreasonable risk to subjects

After evaluating an Unanticipated Adverse Effect, if the principal investigator determines the effect presents an unreasonable risk to subjects, the principal investigator shall terminate the study or parts of the study presenting that risk as soon as possible. Study termination shall occur no later than 5 working days after the principal investigator makes this determination and not later than 15 working days after the principal investigator first received notice of the effect.

Withdrawal of IRB approval

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The Principal investigator shall notify the IRB office and participating investigators of any withdrawal of approval of the study by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

8.4 Medical Monitoring

It is the responsibility of the principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of adverse events.

8.4.1 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review data relevant to safety (not efficacy) after approximately 50% of the subjects have delivered. The DSMB will provide a recommendation as to whether the study should continue without modification of the protocol or informed consent. All unanticipated problems involving risks to participants or others will be reported by Dr. Amanda Roman to the head of the DSMB for this study

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in

source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Records Retention

It is the principal investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10. Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

Research data will be reviewed by the study coordinator for correctness. Research charts will undergo periodic random audits to ensure the integrity of the data. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12. Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.

13. Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the principal investigator. Any investigator involved with this study is obligated to provide the principal investigator with complete test results and all data derived from the study.

14. REFERENCES

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Appendix #1: Initial Follow up

Record ID _____

Date of contact: _____

Method of contact:

- Email
- Phone call
- RedCap Survey
- Text Message
- Other: _____

Name of person contacting participant: _____

Have you experienced any complications with your pregnancy? [] Yes [] No

If yes, please describe: _____

Have you been seen for a problem outside of a regularly scheduled prenatal visit? [] Yes [] No

Was this visit for: _____

Have you been seen on labor and delivery, the labor and delivery triage unit, or the emergency room?
[] Yes [] No; if yes please describe: _____

Have you experienced vaginal bleeding? [] Yes [] No

Have you experienced vaginal discharge? [] Yes [] No

Have you experienced contractions? [] Yes [] No

Have you experienced leaking of fluid? [] Yes [] No

Were you admitted to the hospital? [] Yes [] No

What dates were you admitted? _____

For how many days? _____

Why were you admitted to the hospital? _____

Were you treated with steroid shots for fetal lung maturity? [] Yes [] No

Were you treated with medication to stop preterm contractions or labor? [] Yes [] No

Was the cerclage removed? Why _____

Have you had sexual intercourse since you were enrolled in this study? [] Yes [] No

Additional notes/comments: _____

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Appendix #2 Monthly Follow-Up

Since our last contact with you, have you experienced any complications with your pregnancy?
 Yes No. If yes, please describe: _____

Since our last contact with you, have you been seen for a problem outside of a regularly scheduled prenatal visit? Yes No

Since our last contact with you, have you been seen on labor and delivery, the labor and delivery triage unit, or the emergency room? Yes No . If yes please describe: _____

Since our last contact with you, have you experienced vaginal bleeding? Yes No

Since our last contact with you, have you experienced vaginal discharge? Yes No

Since our last contact with you, have you experienced contractions? Yes No

Since our last contact with you, have you experienced leaking of fluid? Yes No

Were you admitted to the hospital? Yes No

Why were you admitted to the hospital? _____

What dates were you admitted? _____

If yes, for how many days? _____

Were you treated with steroid shots for fetal lung maturity? _____

Were you treated with medication to stop preterm contractions or labor? Yes No

Was the cerclage removed? Why _____

Since our last contact with you, have you had sexual intercourse? Yes No

Additional notes/comments: _____